REMARKS

I. Status of the Specification

The specification has been amended to correct for formal defects. No new matter has been entered by way of these amendments.

II. Status of the Claims

Claims 1, 4, 7-11, 13-15, 17, 20, 21, 24-26, 28-31, 34, 35, 38-40, 42, 43 and 46-50 were pending and examined in the December 29, 2005 Office Action. In this reply, claims 1, 15, 30 and 42 have been amended for clarity. Accordingly, claims 1, 4, 7-11, 13-15, 17, 20, 21, 24-26, 28-31, 34, 35, 38-40, 42, 43 and 46-50 will be pending upon entry of this amendment.

Support for amendments to claims 1, 15, 30 and 42 is found throughout the specification as filed, for example at p. 3, ll. 11-16, p. 4, ll. 30-34, p. 5, ll. 32-34, p. 9, ll. 31-34, and p. 10, ll. 6-9.

III. Rejection Under 35 U.S.C. § 112, ¶ 1 – Written Description

The Examiner rejected claims 1, 4, 7-11, 13-15, 17, 20, 21, 24-26, 28-31, 34, 35, 38-40, 42, 43 and 46-50 as allegedly lacking written description support for the claimed invention. Specifically, the Examiner stated that claims for administering "a donor cell which expresses at least one donor antigen and which contact-dependent helper effector function" "from five to eight days prior to transplantation of the tissue or organ" are not supported. The Examiner reasoned that "generic or a sub-generic disclosure cannot support a species unless the species is specifically described" such that disclosure in the specification of a single or limited species does not provide sufficient direction and guidance to the "limitations" currently claimed (emphasis in Office Action, p. 3, ¶ 4).

Applicant respectfully traverses this rejection.

Applicant respectfully submits that the proposed amendment to the claims obviates, in part, the Examiner's rejections under 35 U.S.C. § 112, ¶ 1 as the rejected claim phrase "a donor cell which expresses at least one donor antigen and which contact-dependent helper effector function" no longer appears in the claims.

Further, Applicant respectfully submits that generic and specific support for the rejected claim term "from five to eight days prior to transplantation of the tissue or organ" *is* found in the specification. For example, the specification explains that, in general, "administration of the allogeneic or xenogeneic cells and antagonist can be performed several days (e.g., five to eight days) prior to tissue or organ transplantation" at p. 10, ll. 15-17. The specification also provides, in connection with Example 1, that "an effective treatment regimen can include initiation of antibody administration prior to tissue or organ transplantation (e.g., five to eight days before transplantation)" at p. 11, ll. 5-7, and that "[a]llogeneic cells were administered to graft recipients by tail vein injection five to eight days prior to islet allograft transplantation" at p. 14, ll. 30-31. Accordingly, administration of allogeneic or xenogeneic cells "from five to eight days prior to transplantation of the tissue or organ" in the context of the specification clearly supports a genus, and not just "possibly a single or limited species" as argued by the Examiner.

In view of the foregoing, it is respectfully submitted that the written description rejection has been obviated or overcome. Accordingly, withdrawal of this rejection is respectfully requested.

IV. Rejections Under 35 U.S.C. § 103 – Obviousness

The Examiner maintained his rejection of claims 1, 4, 7-11, 13-15, 17, 20, 21, 24-26, 28-31, 34, 35, 38-40, 42, 43 and 46-50 as allegedly obvious over Lederman et al. (Lederman) U.S. Patent No. 6,403,091, in view of Beschorner et al. (Beschorner) U.S. Patent No. 5,597,563, Cobbold et al. (Cobbold) U.S. Patent No. 5,690,933, Cornaby et al. (Cornaby) U.S. Patent No. 4,959,301 "essentially for reasons of record" and in further view of newly added Sachs et al. (Sachs) U.S. Patent. No. 6,296,846.

The Examiner argues that the administration of tolerizing agents "from five to eight days" prior to transplantation appears to be well within the variable of an immunosuppressive regimen that achieved a recognized result of inhibiting or preventing graft rejection and of creating a tolerogenic environment in order to achieve long term graft survival as shown by Beschorner, Cobbold, Cornaby, and newly added Sachs (Office Action, dated December 29, 2005, p. 4, ¶11). The Examiner alleges "that where the general conditions or a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experiments" (Office Action, dated December 29, 2005, p. 4, ¶ 2). Specifically, the Examiner alleges that the 5-8 day period is taught by: (1) Beshorner's teaching of the administration of an immunosuppressive agent such as cyclosporine in "about 7 to about 28 days" prior to infusion of tolerogenic antigen presenting cells; (2) Cobbold's teaching of the immunosuppressive effect of anti-T cell antibodies administered 1-7 days prior to exposure to tolerogenic antigen; (3) Cornaby's teaching of the measuring IL-2 levels to determine impending rejection 2-8 days prior to rejection; and (4) Sachs's teaching of pre-conditioning regimes for the transplant regimen to occur between days 1 and 8 prior to engraftment.

Applicant respectfully traverses this rejection.

These references, alone or in combination, do not teach or suggest the following limitations of the claimed method. The limitations for the administration of an "allogeneic or xenogeneic donor cell having a gp39 ligand mediating contact-dependent helper effector function with a recipient T cell" and the administration of these specific tolerizing agents 5-8 days before transplant, as claimed in amended claims 1, 15, 30 and 42, are not taught or suggested by the prior art, taken alone or in combination.

Accordingly, Applicant respectfully submits that the Examiner has not established a case of *prima facie* obviousness of the claimed invention as the cited references alone or in combination do not teach or suggest all the limitations of the claimed method (MPEP § 2142; *In re Royka*, 490 F.2d 981, 984 (C.C.P.A. 1974); *see* amended claims 1, 15, 30 and 42).

Specifically, Lederman, Beschorner, Cobbold, Cornaby, and Sachs, taken alone or in combination, do not teach the claimed administration of an "allogeneic or xenogeneic donor cell having a gp39 ligand mediating contact-dependent helper effector function with a recipient T cell" as claimed in amended claims 1, 15, 30 and 42.

Lederman, Cobbold and Cornaby do not teach or suggest the administration of allogeneic or xenogeneic donor cells. Lederman discloses only the administration of an antibody alone (*see, e.g.*, Lederman, col. 8, ll. 5-5; col. 9, ll. 36-38; col. 10, ll. 14-16 and 28-30; and col. 11, ll. 8-13, etc.). Cobbold discloses only the co-administration of CD4 and CD8 monoclonal antibodies and optional administration of antigens (Cobbold, abstract and col. 3, ll. 15-16 and ll. 39-47). Cornaby discloses only the use of general immunosuppressive drugs, such as cyclosporine (*see, e.g.*, Cornaby, col. 3, ll. 48-50, cols. 17-18, ll. 60-17).

Meanwhile, Beschorner and Sachs merely disclose the administration of antigen presenting cells *incapable* of mediating contact-dependent helper effector function with recipient T cells because antigen is presented in an environment *devoid* of recipient T cells. That is, prior to the administration of antigen presenting cells, Beschorner uses a general immunosuppressive agent (Beschorner, col. 5, ll. 11-13, col. 7, ll. 3-5, and col. 8, ll. 3-13), and Sachs uses an "antibody preparation [that] eliminates mature T cells" (Sachs, col. 6, ll. 7-11). Thus, the cells of Beschorner and Sachs are not "mediating contact-dependent helper effector function with a recipient T cell" as there are no recipient T cells present at the time of administration.

Additionally, Applicant submits that Lederman, Beschorner, Cobbold, Cornaby, and newly added Sachs, taken alone or in combination, do not teach the claimed administration of donor cells and antibodies "from five to eight days prior to transplantation of the tissue or organ" as used in the context of the presently claimed invention. Additionally, none of these references, taken alone or in combination, teach or suggest the administration of *both* "allogeneic or xenogeneic donor cell" and "an anti-human gp39 antibody" in the critical time period "from five to eight days prior to transplantation of the tissue or organ".

Lederman describes antibodies to a T-cell antigen (5c8) which inhibit T-cell activation of B-cells. Lederman does not teach or suggest *any* method or time frame for administration of tolerizing agents prior to transplantation; therefore, Lederman does not make obvious the treatment or time frames of the methods of the claims.

Beschorner teaches administration of an immunosuppressive agent (cyclosporine) relative to administration of a tolerizing agent (tolerogenic APCs). Beschorner does not teach administration of a tolerizing agent relative to administration of a tissue graft. Beschorner does not teach administration of tolerizing agents in any time frame *relative to when the actual donor organ or tissue is transplanted.* Therefore, Beschorner cannot make obvious the 5-8 day treatment period of the claims.

Cobbold teaches a 1-7 day administration of T-cell-depleting antibodies prior to administration of non-T-cell-depleting antibodies (Cobbold, col. 4, ¶ 3). Cobbold does *not* teach a 1-7 day period for administration of antibodies relative to administration of antigen, or administration of tolerizing antibodies and/or antigen relative to time of transplant. There is no teaching or suggestion of administration of immunosuppressive agents and tolerogenic antigen *relative to when the transplant is grafted.*

Cornaby teaches measurement of IL-2 or IL-2 receptor levels as an indicator that graft rejection is 2 to 8 days away. This does not teach administration of tolerizing agents relative to transplant; rather, Cornaby teaches measuring for impending rejection *following* graft transplant. This in no way provides guidance as to treatment regimes for tolerization *prior to* transplant.

Sachs teaches a pre-conditioning treatment involving, *inter alia*, the administering anti-human anti-thymocyte globulin (ATG) to eliminate a recipient's mature T cells and natural killer cells on day 1, followed by sublethal irradiation to the recipient between days 1-8 (Sachs, col. 8, ¶¶ 1-2; *see also* col. 3, ¶ 3). Sachs does not provide a time frame for any pre-conditioning regimes involving the claimed administration of both an "allogeneic or xenogeneic donor cell" and "an anti-human gp39 antibody" in the key time window "from five to eight days prior to transplantation of the tissue or organ" as presently claimed.

Despite the Examiner's contention that the five to eight day administration of the specifically-claimed tolerizing agents appears to be well within the variable of an immunosuppressive regimen that achieved a recognized result of inhibiting or preventing graft rejection, the Examiner does not in fact provide a single immunosuppressive regimen for administration of both tolerizing antibodies and antigen from 5-8 days prior to the transplantation of donor tissues or organs (Office Action, dated December 29, 2005, p. 4, ¶11), let alone anti-gp39 antibodies. Under no combination of Lederman, Beschorner, Cobbold, Cornaby, or Sachs may be found teaching, suggestion, or motivation to administer gp39 antibody and donor cells from 5-8 days prior to the transplantation of donor tissues or organs.

Applicant submits that the teaching or suggestion to make the claimed combination along with a reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure (*In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). The time frame for administration of the tolerizing agents of the claims represents a significant difference in the method of tolerizing transplant recipients. The application provides a critical time frame and sequence for applying donor cells and gp39 antibodies as an immunosuppressive agent, *relative to transplantation of the donor tissue*. Using the methods of the invention as claimed, such a skilled artisan now has the tools in hand to properly tolerize a patient in need of an organ transplant using the gp39 antibodies of the invention.

The cited references do not teach or suggest each and every element of the claimed invention; therefore, a *prima facie* case of obviousness has not been made. Claims 4, 7-11, 13-14, 17, 20-21, 24, 26, 28-29, 31, 34, 35, 38-40, 43, and 46-50 depend from independent claims 1, 15, 30 and 42, and overcome the cited references for at least those same reasons stated above in relation to the independent claims. Accordingly, Applicant respectfully requests that the rejection of claims 1, 4, 7-11, 13-15, 17, 20, 21, 24-26, 28-31, 34, 35, 38-40, 42, 43 and 46-50 as obvious over cited references be withdrawn.

V. Rejections Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1, 4, 7-11, 13-15, 17, 20-21, 24-26, 28-31, 34-35, 38-40, 42-43 and 46-50 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,683,693, claims 1-34 of U.S. Patent No. 5,902,585, and claims 1-7 of U.S. Patent No. 6,375,950.

Applicant respectfully traverses this rejection.

Applicants submit that the claims as amended in the present response are patentably distinct over the claims of the above-identified patents. The claims identified above do not recite a method for inducing T cell non-responsiveness to a donor antigen, or to a donor cell, tissue or organ that expresses at least one such antigen, by administering the tolerizing agents of the invention *from five to eight days prior to transplantation* of the tissue or organ to be transplanted. Administration of tolerizing agents within a five to eight day period prior to transplantation is simply not claimed in the above patents and is not obvious in view of these claims and the prior art. There is no teaching or suggestion of the five to eight day time period. Therefore, Applicants request that the rejection of the claims of the instant invention under the judicially created doctrine of obviousness-type double patenting be withdrawn.

Applicant submits that the Examiner has provided no evidence of a treatment regimen that the parameters of the claimed methods would fall within, including the claims of the above patents. Nor has the Examiner presented evidence that any methods resembling the claimed treatment methods are "well known and practiced by the ordinary artisan" for preventing graft rejection.

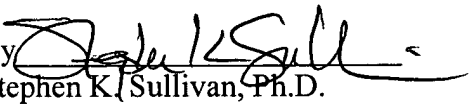
Accordingly, applicant respectfully requests that the rejection of claims 1, 4, 7-11, 13-15, 17, 20-21, 24-26, 28-31, 34-35, 38-40, 42-43 and 46-50 under the judicially created doctrine of obviousness-type double patenting be reconsidered.

CONCLUSION

In view of the above amendments and arguments, Applicant believes the pending application is in condition for allowance.

Dated: March 24, 2006

Respectfully submitted,

By 

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